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**(54) 5-Aryl-3H-1,2,4-triazol-3-ones and their use as anticonvulsants.**

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<b>EP-A- 0 221 485</b>	<b>BE-A- 621 842</b>
<b>DD-A- 153 953</b>	<b>DD-A- 160 447</b>
<b>DE-A- 1 126 882</b>	<b>US-A- 3 514 466</b>

**JOURNAL OF MEDICINAL CHEMISTRY**, vol. 14, no. 3, 1971, pages 260-262; M.Y. MHASAL-KAR et al.: "Further studies in substituted 4H-1,2,4-triazoles for possible hypoglycemic activity"

**SYNTHESIS**, vol. 10, October 1987, pages 912-914; J.M. KANE: "The bis(tricyclohexylstannylyl) sulfide thionation of 3H-1,2,4-triazol-3-ones"

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JOURNAL OF PHARM. SCIENCES, vol. 66, no. 7, July 1977, pages 971-975; S.S. PARMAR et al.: "Anticonvulsant activity and selective inhibition of NAD-dependent oxidations in rat brain homogenates by newer mercapto-triazoles"

RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, vol. 37, no. 3, September 1982, pages 499-502; R.K. JAISWAL et al.: "Anticonvulsant activity and monoamine oxidase inhibitory properties of substituted 1,2,4-triazoles"

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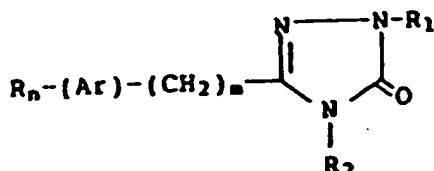
**Description**

This invention relates to the use of 5-aryl-3H-1,2,4-triazol-3-ones for preparing a medicament for treatment of seizure disorders.

- 5 M.Y. Mhasalkar, et al., (J. Med. Chem. 14, 260-262, 1971) teach that a compound of formula I has hypoglycemic activity. U.S.-A-3,514,466; BE-A-621,842 and DE-A-1,126,882 teach that various compounds of formula I have sedative and hypnotic activity. ZA 65/1537 and NL 6504121 teach that some compounds of formula I have anti-inflammatory, antipyretic and analgetic activity. DD-A-160,447; DD-A-153,953 and BE-A-894,856 teach that some compounds of formula I are herbicides. U.S.-A-4,414,221 teaches that some 10 compounds of formula I are insecticides and acaricides. JP 50-63119 teaches that some compounds of formula I have anticoccidial activity.

More specifically this invention relates to the use of a compound of the formula:

15



20

I

wherein

- Ar represents phenyl, naphthyl or an aromatic heterocyclic moiety, selected from 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, N-(C<sub>1-6</sub> alkyl)-pyrrolyl, 6-isoquinolyl, 6-quinolyl and 3-quinolyl,  
25 R<sub>1</sub> is hydrogen or C<sub>1-6</sub> alkyl,  
R<sub>2</sub> is C<sub>1-6</sub> alkyl,  
R is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, halogeno, or trifluoromethyl, and  
n is zero, 1 or 2, or  
30 R<sub>n</sub>-(Ar) is methylenedioxophenyl, and  
m is zero, 1 or 2,  
and the pharmaceutically acceptable salts of the compounds wherein Ar is a nitrogen-containing heterocyclic moiety for preparing a medicament for treating seizure disorders.

For R, preferably halogeno represents chloro or fluoro, and methyl and ethyl represent the preferred 35 C<sub>1-C<sub>6</sub></sub> alkyl moieties, although all the straight, branched and cyclic manifestations thereof such as n-propyl, cyclopentyl, cyclohexyl and cyclopropyl are herein included. C<sub>1-C<sub>6</sub></sub> alkoxy radicals include ethers having alkyl moieties paralleling the C<sub>1-C<sub>6</sub></sub> alkyl group.

R<sub>1</sub> and R<sub>2</sub> are preferably methyl or ethyl, although any straight or branched C<sub>1-C<sub>6</sub></sub> alkyl group may be used.

40 When "Ar" is phenyl, preferably n is one, representing a mono-substituted phenyl moiety with the R-substituent being a group located at any of the ortho, meta or para positions, although the ortho- and para-substituted compounds are preferred. When Ar is disubstituted (i.e., n is 2), the 2,3-; 2,4-; 2,5-; 2,6-; 3,4-; and 3,5- positions are contemplated. The tautomeric forms are included for each of the compounds embraced within formula I. Except when Ar is phenyl, it is preferred that m is zero. When Ar is phenyl it is preferred that m is zero or one.

45 When "Ar" of formula I represents a heterocyclic moiety such heterocyclic moieties as 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, N-(C<sub>1-6</sub> alkyl)-pyrrolyl, 6-isoquinolyl, 6-quinolyl and 3-quinolyl are contemplated. Preferred is 4-pyridyl, with or without an R substituent. State of the art salts formed with the heterocyclic moieties are generally employed, with the hydrochloride being one of 50 convenience and general applicability: such salts being formed by standard techniques well known in the art.

When "Ar" represents naphthyl, the preferred isomer is 2-naphthyl with the R moiety being attached thereto at any of the available positions, although positions 5-, 6-, 7- or 8- are preferred for either the mono- or di-R-substituted naphthyl compounds of formula I.

55 Another object of the present invention is represented by a compound of formula I wherein:

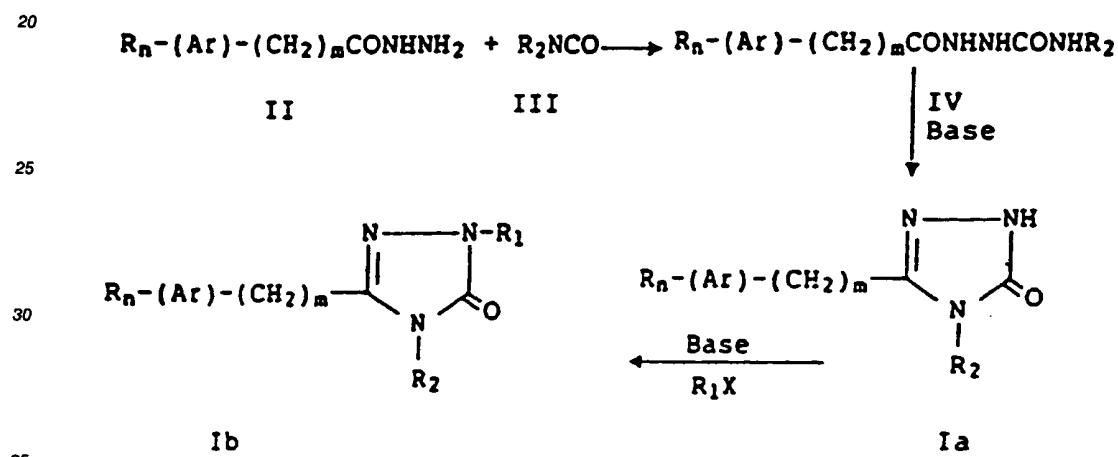
Ar represents phenyl, naphthyl, or an aromatic heterocyclic moiety selected from 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, N-(C<sub>1-6</sub> alkyl)-pyrrolyl, 6-isoquinolyl, 6-quinolyl and 3-quinolyl.

$R_1$  is hydrogen or  $C_{1-6}$  alkyl,  
 $R_2$  is  $C_{1-6}$  alkyl,  
 $R$  is  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, hydroxy, halogeno, or trifluoromethyl, and  
 $n$  is 1 or 2, or  
5      $R_{n'}(Ar)$  is methylenedioxyphenyl, and  
 $m$  is zero, 1 or 2

with the proviso that when  $R_n$ -(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 4-chlorophenyl and R<sub>2</sub> represents ethyl, R<sub>1</sub> cannot represent hydrogen, and when R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents phenyl and R<sub>1</sub> represents methyl, R<sub>2</sub> cannot represent methyl or ethyl,  
10 and the pharmaceutically acceptable salts of the compounds wherein Ar is a nitrogen-containing heterocyclic moiety for use as a medicament.

A further object of the present invention is represented by the compounds of formula I wherein  $R_n$ -(Ar)-(CH<sub>2</sub>)<sub>m</sub>- represents 4-chlorophenyl, R<sub>1</sub> represents methyl and R<sub>2</sub> represents ethyl or wherein  $R_n$ -(Ar)-(CH<sub>2</sub>)<sub>m</sub>- represents 2-chlorophenyl, R<sub>1</sub> represents hydrogen and R<sub>2</sub> represents methyl.

**15** The compounds of Formula I may readily be prepared using processes and techniques analogously known in the art, for example in the method of S. Kuboda and M. Uda, Chem. Pharm. Bull. **21**, 1342 (1979), as seen by the following reaction scheme:



wherein  $R_n$ -(Ar)-(CH<sub>2</sub>)<sub>m</sub>- , R<sub>1</sub> and R<sub>2</sub> are as defined in formula I, and X is a suitable leaving group.

The preparation of the 1-arylsemicarbazides (IV) is readily effected by reacting an aryl hydrazide (II) with an R<sub>2</sub>-substituted isocyanate (III) by contacting the reactants together in a suitable aprotic solvent, preferably one in which the hydrazide reactant is soluble, e.g., tetrahydrofuran (THF), CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, benzene, toluene, Et<sub>2</sub>O and the like. The reaction is quite rapid and may be carried out at 0 °C to about room temperature and, although the reaction proceeds rapidly, the mixture may be left for 24 hours without any significant decrease in yield. The required hydrazides and isocyanates are readily available but may be prepared by known techniques quite obvious to one of ordinary skill in the art.

The desired 5-aryl-2,4-dihydro-3H-1,2,4-triazol-3-ones (**Ia**) may be prepared by reacting the semicarbazides (**IV**) with a base, preferably an aqueous alkali metal hydroxide (e.g., NaOH, KOH) at about 50-120 °C, although reflux temperatures are preferred. Normal reaction time is about 7 hours, although 4-24 hours may be needed depending on the temperature of the mixture.

The desired 2,4-disubstituted-2,4-dihydro-3H-1,2,4-triazol-3-ones (Ib) may be prepared by reacting the 4-substituted-2,4-dihydro-3H-1,2,4-triazol-3-ones (Ia) with an appropriate R<sub>1</sub>X reactant wherein X is a suitable leaving group, e.g., Cl, Br, OSO<sub>2</sub>CF<sub>3</sub> and the like. Preferably the reaction takes place in a solution of an aqueous alkali metal hydroxide, (e.g., KOH, NaOH) although more reactive bases (e.g., NaH, KH, LDA) may be used if the reaction is effected under aprotic dry conditions. The reaction preferably takes place at room temperature over periods of about 18 hours to two weeks.

55 The following specific examples are given to illustrate the preparation of the compounds

Preparation of Intermediate 1-Aroyl-4-substituted semicarbazidesEXAMPLE 15    1-(4-Chlorobenzoyl)-4-ethylsemicarbazide

A stirred suspension of 4-chlorobenzoic acid, hydrazide (17.1 g,  $1.00 \times 10^{-1}$  mole), and THF (425 ml) was warmed until homogeneous, at which time ethyl isocyanate (8.7 ml,  $1.1 \times 10^{-1}$  mole) was added via syringe. A precipitate soon formed. After stirring overnight the reaction was diluted with  $\text{Et}_2\text{O}$  and the precipitate was collected by filtration affording a colorless powder: 23.7 g (98%). Crystallization from ethanol gave a colorless solid: 21.4 g (88%), mp 237-239°.

EXAMPLE 215    1-(4-Pyridoyl)-4-methylsemicarbazide

When, in the procedure of Example 1, isonicotinic acid is substituted for 4-chlorobenzoic acid, the title compound is obtained.

20    Preparation of 5-Aryl-4-substituted-2,4-dihydro-3H-1,2,4-triazol-3-onesEXAMPLE 325    5-(4-Chlorophenyl)-2,4-dihydro-4-ethyl-3H-1,2,4-triazol-3-one

1-(4-chlorobenzoyl)-4-ethylsemicarbazide (23.7 g,  $9.81 \times 10^{-2}$  mole) and 1 molar aqueous NaOH (118 ml,  $1.18 \times 10^{-1}$  mole) were stirred and warmed to reflux. After refluxing 23 hours, heating was discontinued and the reaction was acidified by the dropwise addition of 1 molar aqueous hydrochloric acid (130 ml,  $1.30 \times 10^{-1}$  mole). A colorless solid formed as the reaction was acidified and, after cooling in an ice bath, this was collected by filtration. Crystallization from isopropanol gave colorless spars: 18.2 g (83%), mp 188-189°.

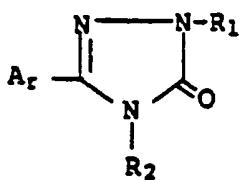
EXAMPLE 435    2,4-Dihydro-4-methyl-5-(4-pyridinyl)-3H-1,2,4-triazol-3-one

When, in the procedure of Example 3, 1-(4-pyridoyl)-4-methylsemicarbazide is substituted for 1-(4-chlorobenzoyl)-4-ethylsemicarbazide, the title compound is obtained. Mp 249-251 °C.

40    Preparation of 5-Aryl-2,4-dihydro-2,4-disubstituted-3H-1,2,4-triazol-3-onesEXAMPLE 545    5-(4-Chlorophenyl)-2,4-dihydro-4-ethyl-2-methyl-3H-1,2,4-triazol-3-one

To a stirred, room temperature solution of 5-(4-chlorophenyl)-2,4-dihydro-4-ethyl-3H-1,2,4-triazol-3-one (6.00 g,  $2.68 \times 10^{-2}$  mole) and 1 molar aqueous NaOH (30.0 ml,  $3.00 \times 10^{-2}$  mole) was added a solution of methyl iodide (2.5 ml,  $4.0 \times 10^{-2}$  mole) and ethanol (10 ml). After stirring overnight at room temperature, the reaction mixture was transferred to a separatory funnel where it was extracted three times with EtOAc. The EtOAc extracts were combined, washed with saturated aqueous NaCl, and dried over  $\text{Na}_2\text{SO}_4$ . The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving an oil which slowly solidified. Chromatography and crystallization from cyclohexane gave small colorless needles: 3.4 g (53%), mp 73-75°.

In a similar manner the following compounds also may be prepared.



	$\text{A}_r$	$\text{R}_1$	$\text{R}_2$	mp (°C)
15	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	177-178
	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	140-141
	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	87-89
	C <sub>6</sub> H <sub>5</sub>	H	C <sub>2</sub> H <sub>5</sub>	163-165
	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	oil
20	2-ClC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	168-170
	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	61-63
	4-ClC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	213-215
	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	126-128
	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	79-81
25	4-CIC <sub>6</sub> H <sub>4</sub>	H	C <sub>2</sub> H <sub>5</sub>	188-189
	4-CIC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	73-75
	4-CIC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	62-64
	4-CIC <sub>6</sub> H <sub>4</sub>	n-C <sub>3</sub> H <sub>7</sub>	C <sub>2</sub> H <sub>5</sub>	oil
	2-FC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	189-191
30	2-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	69-71
	4-FC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	216-218
	4-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	104-106
	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	CH <sub>3</sub>	170-172
	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	107-109
35	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	206-208
	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	92-94
	4-CH <sub>3</sub> O-3-(n-C <sub>4</sub> H <sub>9</sub> O)C <sub>6</sub> H <sub>3</sub>	H	CH <sub>3</sub>	96-98
	4-CH <sub>3</sub> O-3-(n-C <sub>4</sub> H <sub>9</sub> O)C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	112-114
	4-CH <sub>3</sub> O-3-(cyclo-C <sub>5</sub> H <sub>9</sub> O)C <sub>6</sub> H <sub>3</sub>	H	CH <sub>3</sub>	184-186
40	4-CH <sub>3</sub> O-3-(cyclo-C <sub>5</sub> H <sub>9</sub> O)C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	153-155

The pharmacological profile of these compounds and their relative potencies may readily be demonstrated through standard laboratory tests indicative of compounds known to be useful as anticonvulsants suitable for use in the treatment of seizure disorders, particularly idiopathic epilepsy.

45 For example, in the evaluation and characterization of the anticonvulsant and GABAergic activity and to observe a suitable pharmacological profile of the compounds of this invention, it is convenient to employ such tests as the antagonism of 3-mercaptopropionic acid-induced convulsions, an assay performed on mice wherein wild running fits or generalized seizures are induced by 3-mercaptopropionic acid; the antagonism of strychnine-induced seizures in mice; the antagonism to maximal electroshock, an assay performed in mice wherein seizures are caused by the administration of electroshock; and the antagonism to pentylenetetrazol, an assay to measure the prevention of seizures caused by administration of pentylenetetrazol.

50 Compounds which inhibit pentylenetetrazol-induced seizures in mice are known to possess anticonvulsant and anti-anxiety effects. An appropriate dose of test compound is administered to groups of mice and, at a selected time thereafter, pentylenetetrazol, prepared as a solution in distilled water such that 10 ml/kg delivers a dose of 60 mg/kg, is administered by rapid intravenous injection. Absence of clonic convulsions for 2 minutes after pentylenetetrazol is considered significant protection. Prevention of tonic extensor convulsions is also reported and usually occurs at a dose lower than that required to block clonic

convulsions. Inhibition of clonic seizures induced by this dose of pentylenetetrazol is evidence of potential anticonvulsant/anti-anxiety activity. Against seizures caused by pentylenetetrazol, 5-(4-chlorophenyl)-2,4-dihydro-4-ethyl-2-methyl-3H-1,2,4-triazol-3-one has an ED<sub>50</sub> of 16.5 mg/kg.

Based upon standard laboratory methodology (including comparative tests with known anticonvulsants),

5 the compounds of this invention will exert anticonvulsant activity useful in the treatment of idiopathic epilepsy at oral dosage levels of about 0.25 to 25 mg/kg of body weight per day. Of course the degree of severity of the disease, age of the patient and other factors normally considered by the attending diagnostician will influence the individual regimen for each patient. In general, the parenterally administered doses are about 1/4 to 1/2 that of the orally administered dose.

10 For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. The solid unit dosage forms can be a capsule which can be of the ordinary gelatin type containing, for example, lubricants and inert fillers such as lactose, sucrose or cornstarch. In another embodiment the compounds of general formula I can be tableted with conventional tablet bases such as lactose, sucrose and cornstarch, in combination with binders such as acacia, cornstarch or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

15 For parenteral administration, the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water, alcohol, oils and other acceptable organic solvents, with or without the 20 addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanol, glycols such as propylene glycol or polyethylene glycol, or 2-pyrrolidone are preferred liquid carriers, particularly for injectable solutions.

25 The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic®, a silicone rubber manufactured by the Dow-Corning Corporation.

30 As is true for most classes of compounds generally suitable as therapeutic agents, certain subgeneric groups and specific members of that class, in the light of their overall biological profile, are preferred. In this instance those compounds wherein m is zero are preferred, with those wherein m is one being next preferred. The preferred Ar moiety is phenyl. The preferred R substituent is chloro, with the chloro being at 35 the 2- or 4-positions of the aromatic moiety being preferred. It is preferred to have an alkyl substituent at both of the R<sub>1</sub> and R<sub>2</sub> positions with methyl and ethyl being the preferred groups. Particularly preferred compounds are

5-(4-chlorophenyl)-2,4-dihydro-4-ethyl-2-methyl-3H-1,2,4-triazol-3-one

5-(4-chlorophenyl)-2,4-diethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

40 5-(2-chlorophenyl)-2,4-dihydro-4-methyl-3H-1,2,4-triazol-3-one

5-(2-chlorophenyl)-2,4-dihydro-2,4-dimethyl-3H-1,2,4-triazol-3-one.

In the present description and claims the term therapeutic "treatment" includes any kind of treatment such as prophylaxis and cure.

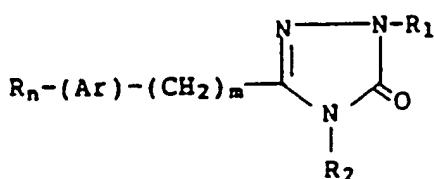
#### 45 Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

#### 1. Use of a compound of the formula

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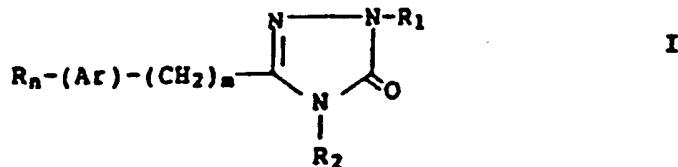
wherein

- Ar represents phenyl, naphthyl, or an aromatic heterocyclic moiety selected from 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, N-(C<sub>1-6</sub> alkyl)-pyrrolyl, 6-isoquinolyl, 6-quinolyl and 3-quinolyl,  
 5 R<sub>1</sub> is hydrogen or C<sub>1-6</sub> alkyl,  
 R<sub>2</sub> is C<sub>1-6</sub> alkyl,  
 R is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, halogeno, or trifluoromethyl, and  
 n is zero, 1 or 2, or  
 10 R<sub>n</sub>-(Ar) is methylenedioxyphenyl, and  
 m is zero, 1 or 2,

and the pharmaceutically acceptable salts of the compounds wherein Ar is a nitrogen-containing heterocyclic moiety, for preparing a medicament for treating seizure disorders.

2. Use of a compound of claim 1 wherein Ar in said compound represents phenyl.  
 15 3. Use of a compound of claim 1 or 2 wherein m in said compound represents zero.  
 4. Use of a compound of claim 1, 2 or 3 wherein R<sub>1</sub> in said compound represents C<sub>1-6</sub> alkyl.  
 20 5. Use of a compound of claim 1, 2 or 3 wherein R<sub>1</sub> in said compound represents methyl or ethyl.  
 6. Use of a compound of claim 1 wherein Ar in said compound is phenyl, m is zero and R is halogeno.  
 25 7. Use of a compound of claim 6 wherein R in said compound is chloro.  
 8. Use of a compound of claim 1 wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-in said compound represents 4-chlorophenyl, R<sub>1</sub> is methyl and R<sub>2</sub> is ethyl.  
 30 9. Use of a compound of claim 1 wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-in said compound represents 4-chlorophenyl, R<sub>1</sub> is hydrogen and R<sub>2</sub> is ethyl.  
 10. Use of a compound of claim 1 wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-in said compound represents 2-chlorophenyl, R<sub>1</sub> is hydrogen and R<sub>2</sub> is methyl.

- 35 11. A compound of the formula



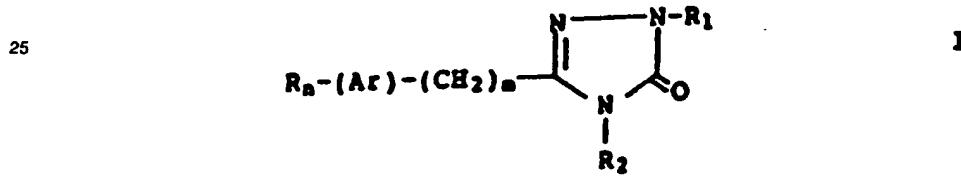
wherein

- Ar represents phenyl, naphthyl, or an aromatic heterocyclic moiety selected from 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, N-(C<sub>1-6</sub> alkyl)-pyrrolyl, 6-isoquinolyl, 6-quinolyl and 3-quinolyl,  
 50 R<sub>1</sub> is hydrogen or C<sub>1-6</sub> alkyl,  
 R<sub>2</sub> is C<sub>1-6</sub> alkyl,  
 R is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, halogeno, or trifluoromethyl, and  
 n is 1 or 2, or  
 55 R<sub>n</sub>-(Ar) is methylenedioxyphenyl, and  
 m is zero, 1 or 2,

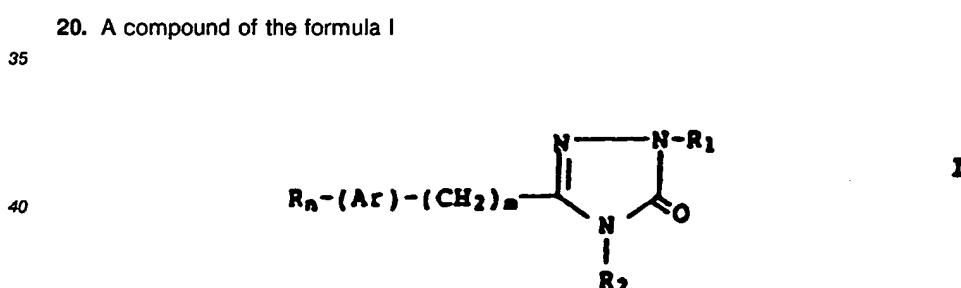
with the proviso that when R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 4-chlorophenyl and R<sub>2</sub> represents ethyl, R<sub>1</sub> cannot represent hydrogen, and when R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents phenyl and R<sub>1</sub> represents methyl, R<sub>2</sub> cannot

represent methyl or ethyl,  
and the pharmaceutically acceptable salts of the compounds wherein Ar is a nitrogen-containing heterocyclic moiety for use as a medicament.

- 5    12. A compound of claim 11 wherein Ar is phenyl.
- 13. A compound of claim 11 or 12 wherein m is zero.
- 14. A compound of claim 11, 12, or 13 wherein R<sub>2</sub> is methyl or ethyl.
- 10    15. A compound of claim 11 wherein Ar is phenyl, m is zero and R is halogeno.
- 16. A compound of claim 15 wherein R is chloro.
- 15    17. A compound of claim 11 wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 2-chlorophenyl, R<sub>1</sub> is hydrogen and R<sub>2</sub> is methyl.
- 18. A compound of claim 11 wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 4-chlorophenyl, R<sub>1</sub> is methyl and R<sub>2</sub> is ethyl.
- 20    19. A compound of the formula I



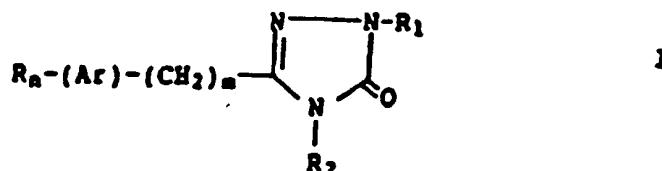
wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 4-chlorophenyl, R<sub>1</sub> is methyl and R<sub>2</sub> is ethyl.



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- wherein R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-represents 2-chlorophenyl, R<sub>1</sub> is hydrogen and R<sub>2</sub> is methyl.
21. A pharmaceutical formulation containing a compound of any one of claims 11 to 20 in admixture with a pharmaceutically acceptable carrier.
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## 22. A process for preparing a compound of the formula

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wherein

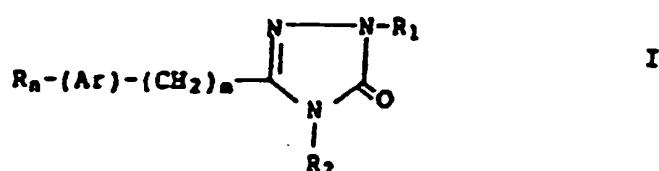
15  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - represents 4-chlorophenyl,  $R_1$  represents methyl and  $R_2$  represents ethyl, which comprises reacting a semicarbazide of formula IV



20 wherein  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - is as defined above, with a base at about 50 °C-120 °C; and transforming the obtained intermediate wherein  $R_1$  represents hydrogen into the compound of formula I by reacting it with a compound of formula  $R_1X$  wherein X is a good leaving group and  $R_1$  is methyl.

## 23. A process for preparing a compound of the formula

25



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wherein

35  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - represents 2-chlorophenyl,  $R_1$  represents hydrogen and  $R_2$  represents methyl, which comprises reacting a semicarbazide of formula IV



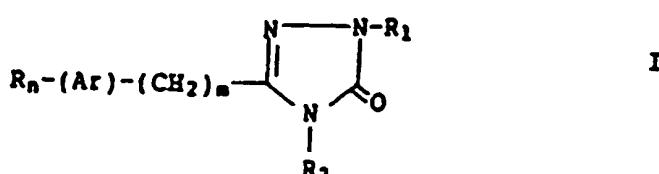
40 wherein  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - is as defined above, with a base at about 50 °C-120 °C.

## Claims for the following Contracting State : ES

## 1. A process for preparing a compound of the formula

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wherein

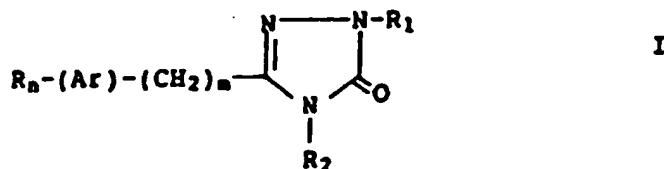
$R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - represents 4-chlorophenyl,  $R_1$  represents methyl and  $R_2$  represents ethyl, which comprises reacting a semicarbazide of formula IV

$R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m\text{CONHNHCONHR}_2$

wherein  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - is as defined above, with a base at about 50 °C-120 °C; and transforming the obtained intermediate wherein  $R_1$  represents hydrogen into the compound of formula I by reacting it with a compound of formula  $R_1X$  wherein X is a good leaving group and  $R_1$  is methyl.

2. A process for preparing a compound of the formula

10



15

wherein

$R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - represents 2-chlorophenyl,  $R_1$  represents hydrogen and  $R_2$  represents methyl, which comprises reacting a semicarbazide of formula IV

$R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m\text{CONHNHCONHR}_2$

wherein  $R_n\text{-}(Ar)\text{-(CH}_2\text{)}_m$ - is as defined above, with a base at about 50 °C-120 °C.

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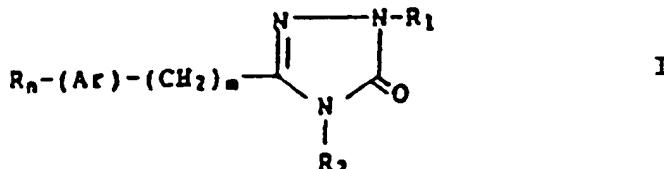
**Patentansprüche**

**Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE**

1. Verwendung einer Verbindung der Formel

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in der

Ar eine Phenyl-, Naphthylgruppe oder eine aromatische, heterocyclische Einheit bedeutet, ausgewählt aus einer 2-, 3- oder 4-Pyridyl-, 2- oder 3-Furyl-, 2- oder 3-Thienyl-, 2- oder 3-Pyrrolylgruppe, einem  $N\text{-}(C_{1-6}\text{-Alkyl})$ pyrrolylrest, einer 6-Isochinolyl-, 6-Chinolyl- und 3-Chinolylgruppe,

$R_1$  ein Wasserstoffatom oder ein  $C_{1-6}$ -Alkylrest ist,

$R_2$  ein  $C_{1-6}$ -Alkylrest ist,

$R$  ein  $C_{1-6}$ -Alkyl-,  $C_{1-6}$ -Alkoxyrest, eine Hydroxylgruppe, ein Halogenatom oder eine Trifluormethylgruppe ist, und

n null, 1 oder 2 ist, oder

$R_n\text{-}(Ar)$  eine Methylendioxyphenylgruppe ist, und

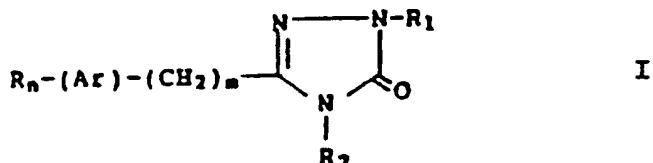
m null, 1 oder 2 ist,

und der pharmazeutisch verträglichen Salze der Verbindungen, in denen Ar eine Stickstoff-enthaltende, heterocyclische Einheit ist, zur Herstellung eines Arzneimittels zur Behandlung von Anfallserkrankungen.

55 2. Verwendung einer Verbindung nach Anspruch 1, wobei Ar in der Verbindung eine Phenylgruppe bedeutet.

3. Verwendung einer Verbindung nach Anspruch 1 oder 2, wobei m in der Verbindung null ist.

4. Verwendung einer Verbindung nach Anspruch 1, 2 oder 3, wobei R<sub>1</sub> in der Verbindung einen C<sub>1</sub>-6-Alkylrest bedeutet.
5. Verwendung einer Verbindung nach Anspruch 1, 2 oder 3, wobei R<sub>1</sub> in der Verbindung eine Methyl- oder Ethylgruppe bedeutet.
6. Verwendung einer Verbindung nach Anspruch 1, wobei Ar in der Verbindung eine Phenylgruppe ist, m null ist, und R ein Halogenatom ist.
- 10 7. Verwendung einer Verbindung nach Anspruch 6, wobei R in der Verbindung ein Chloratom ist.
8. Verwendung einer Verbindung nach Anspruch 1, wobei R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>- in der Verbindung eine 4-Chlorphenylgruppe bedeutet, R<sub>1</sub> eine Methylgruppe ist, und R<sub>2</sub> eine Ethylgruppe ist.
- 15 9. Verwendung einer Verbindung nach Anspruch 1, wobei R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>- in der Verbindung eine 4-Chlorphenylgruppe bedeutet, R<sub>1</sub> ein Wasserstoffatom ist, und R<sub>2</sub> eine Ethylgruppe ist.
10. Verwendung einer Verbindung nach Anspruch 1, wobei R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>- in der Verbindung eine 2-Chlorphenylgruppe bedeutet, R<sub>1</sub> ein Wasserstoffatom ist, und R<sub>2</sub> eine Methylgruppe ist.
- 20 11. Verbindung der Formel



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in der

Ar eine Phenyl-, Naphthylgruppe oder eine aromatische, heterocyclische Einheit bedeutet, ausgewählt aus einer 2-, 3- oder 4-Pyridyl-, 2- oder 3-Furyl-, 2- oder 3-Thienyl-, 2- oder 3-Pyrrolylgruppe, einem N-(C<sub>1</sub>-6-Alkyl)pyrrolylrest, einer 6-Isochinolyl-, 6-Chinolyl- und 3-Chinolylgruppe,

35 R<sub>1</sub> ein Wasserstoffatom oder ein C<sub>1</sub>-6-Alkylrest ist,  
R<sub>2</sub> ein C<sub>1</sub>-6-Alkylrest ist,

R ein C<sub>1</sub>-6-Alkyl-, C<sub>1</sub>-6-Alkoxyrest, eine Hydroxylgruppe, ein Halogenatom oder eine Trifluormethylgruppe ist, und

40 n 1 oder 2 ist, oder

R<sub>n</sub>-(Ar) eine Methylenedioxyphenylgruppe ist, und

m null, 1 oder 2 ist,

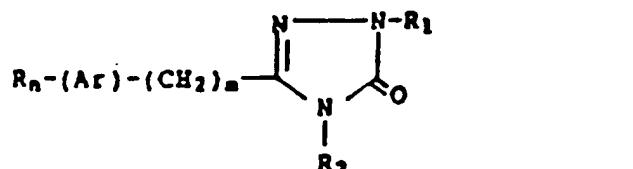
mit der Maßgabe, daß R<sub>1</sub> kein Wasserstoffatom bedeuten kann, wenn R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>- eine 4-Chlorphenylgruppe bedeutet und R<sub>2</sub> eine Ethylgruppe bedeutet, und R<sub>2</sub> keine Methyl- oder Ethylgruppe

45 bedeuten kann, wenn R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>- eine Phenylgruppe bedeutet und R<sub>1</sub> eine Methylgruppe bedeutet, und die pharmazeutisch verträglichen Salze der Verbindungen, in denen Ar eine Stickstoff-enthaltende, heterocyclische Einheit ist, zur Verwendung als Arzneimittel.

12. Verbindung nach Anspruch 11, wobei Ar eine Phenylgruppe ist.
- 50 13. Verbindung nach Anspruch 11 oder 12, wobei m null ist.
14. Verbindung nach Anspruch 11, 12 oder 13, wobei R<sub>2</sub> eine Methyl- oder Ethylgruppe ist.
- 55 15. Verbindung nach Anspruch 11, wobei Ar eine Phenylgruppe ist, m null ist, und R ein Halogenatom ist.
16. Verbindung nach Anspruch 15, wobei R ein Chloratom ist.

17. Verbindung nach Anspruch 11, wobei  $R_n-(Ar)-(CH_2)_m$ - eine 2-Chlorphenylgruppe bedeutet,  $R_1$  ein Wasserstoffatom ist, und  $R_2$  eine Methylgruppe ist.
- 5 18. Verbindung nach Anspruch 11, wobei  $R_n-(Ar)-(CH_2)_m$ - eine 4-Chlorphenylgruppe bedeutet,  $R_1$  eine Methylgruppe ist, und  $R_2$  eine Ethylgruppe ist.
19. Verbindung der Formel I

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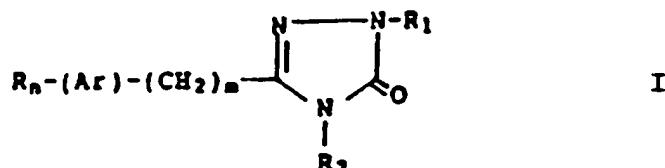


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in der  $R_n-(Ar)-(CH_2)_m$ - eine 4-Chlorphenylgruppe bedeutet,  $R_1$  eine Methylgruppe ist, und  $R_2$  eine Ethylgruppe ist.

- 20 20. Verbindung der Formel I

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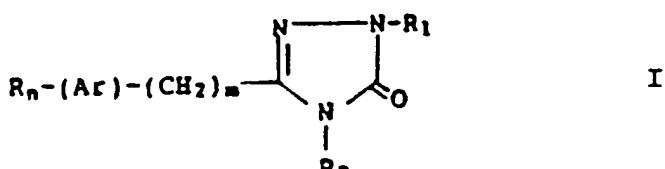
30

in der  $R_n-(Ar)-(CH_2)_m$ - eine 2-Chlorphenylgruppe bedeutet,  $R_1$  ein Wasserstoffatom ist, und  $R_2$  eine Methylgruppe ist.

- 35 21. Arzneimittelformulierung mit einer Verbindung nach einem der Ansprüche 11 bis 20 im Gemisch mit einem pharmazeutisch verträglichen Träger.

22. Verfahren zur Herstellung einer Verbindung der Formel

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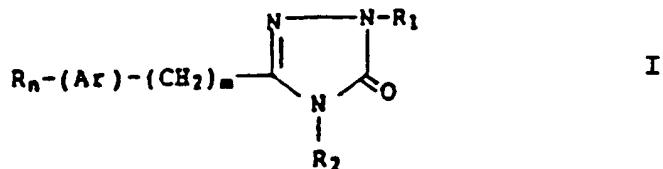
in der  
 $R_n-(Ar)-(CH_2)_m$ - eine 4-Chlorphenylgruppe bedeutet,  $R_1$  eine Methylgruppe bedeutet, und  $R_2$  eine Ethylgruppe bedeutet, das die Umsetzung eines Semicarbazids der Formel IV



- 50 55 in der  $R_n-(Ar)-(CH_2)_m$ - wie vorstehend definiert ist, mit einer Base bei etwa 50°C-120°C und die Umwandlung der erhaltenen Zwischenverbindung, in der  $R_1$  ein Wasserstoffatom bedeutet, in die Verbindung der Formel I umfaßt, wobei sie mit einer Verbindung der Formel  $R_1X$  umgesetzt wird, in der X eine gute Austrittsgruppe ist, und  $R_1$  eine Methylgruppe ist.

## 23. Verfahren zur Herstellung einer Verbindung der Formel

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in der

$R_n\text{-}(Ar)\text{-}(CH_2)_m$ - eine 2-Chlorphenylgruppe bedeutet,  $R_1$  ein Wasserstoffatom bedeutet, und  $R_2$  eine Methylgruppe bedeutet, das die Umsetzung eines Semicarbazids der Formel IV

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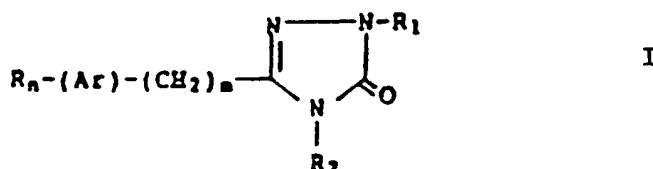
$R_n\text{-}(Ar)\text{-}(CH_2)_m\text{CONHNHCONHR}_2$

in der  $R_n\text{-}(Ar)\text{-}(CH_2)_m$ - wie vorstehend definiert ist, mit einer Base bei etwa  $50^\circ\text{C}$ - $120^\circ\text{C}$  umfaßt.

## 20 Patentansprüche für folgenden Vertragsstaat : ES

## 1. Verfahren zur Herstellung einer Verbindung der Formel

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in der

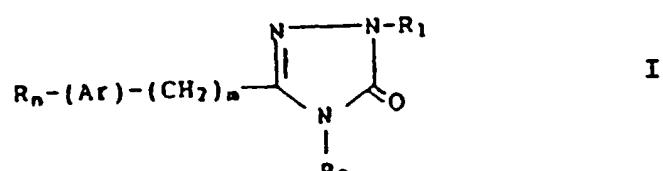
$R_n\text{-}(Ar)\text{-}(CH_2)_m$ - eine 4-Chlorphenylgruppe bedeutet,  $R_1$  eine Methylgruppe bedeutet, und  $R_2$  eine Ethylgruppe bedeutet, das die Umsetzung eines Semicarbazids der Formel IV

$R_n\text{-}(Ar)\text{-}(CH_2)_m\text{CONHNHCONHR}_2$

in der  $R_n\text{-}(Ar)\text{-}(CH_2)_m$ - wie vorstehend definiert ist, mit einer Base bei etwa  $50^\circ\text{C}$ - $120^\circ\text{C}$  und die Umwandlung der erhaltenen Zwischenverbindung, in der  $R_1$  ein Wasserstoffatom bedeutet, in die Verbindung der Formel I umfaßt, wobei sie mit einer Verbindung der Formel  $R_1X$  umgesetzt wird, in der X eine gute Austrittsgruppe ist, und  $R_1$  eine Methylgruppe ist.

## 45 2. Verfahren zur Herstellung einer Verbindung der Formel

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in der

$R_n\text{-}(Ar)\text{-}(CH_2)_m$ - eine 2-Chlorphenylgruppe bedeutet,  $R_1$  ein Wasserstoffatom bedeutet, und  $R_2$  eine Methylgruppe bedeutet, das die Umsetzung eines Semicarbazids der Formel IV



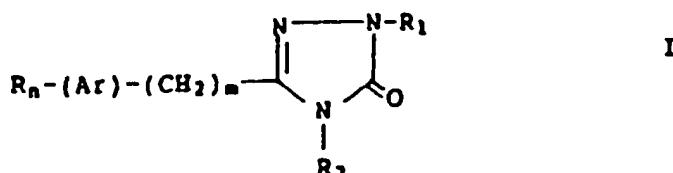
in der  $R_n-(Ar)-(CH_2)_m$ - wie vorstehend definiert ist, mit einer Base bei etwa 50 °C-120 °C umfaßt.

5 Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Utilisation d'un composé de formule :

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dans laquelle

20 Ar représente un groupe phényle, naphtyle ou une portion hétérocyclique aromatique choisie parmi les suivantes :

2- , 3- ou 4-pyridyle, 2- ou 3-furyle, 2- ou 3-thiényle, 2- ou 3-pyrrolyle, N-(C<sub>1-6</sub> alkyl)-pyrrolyle, 6-isoquinolyle, 6-quinolyle et 3-quinolyle,

25 R<sub>1</sub> est l'hydrogène ou C<sub>1-6</sub> alkyle,

R<sub>2</sub> est C<sub>1-6</sub> alkyle,

R est C<sub>1-6</sub> alkyle, C<sub>1-6</sub> alcoxy, hydroxy, halogéno ou trifluorométhyle, et

n est 0, 1 ou 2, ou

R<sub>n</sub>-(Ar) est méthylènedioxyphényle, et

m est 0, 1 ou 2,

30 et des sels pharmaceutiquement acceptables des composés dans lesquels Ar est une portion hétérocyclique contenant de l'azote, pour la préparation d'un médicament pour le traitement des désordres de crises.

35 2. Utilisation d'un composé selon la revendication 1, selon laquelle Ar dans ledit composé représente un groupe phényle.

3. Utilisation d'un composé selon la revendication 1 ou 2, selon laquelle m dans ledit composé représente 0.

40 4. Utilisation d'un composé selon la revendication 1, 2 ou 3, selon laquelle R<sub>1</sub> dans ledit composé représente un groupe C<sub>1-6</sub> alkyle.

5. Utilisation d'un composé selon la revendication 1, 2 ou 3, selon laquelle R<sub>1</sub> dans ledit composé représente un groupe méthyle ou éthyle.

45 6. Utilisation d'un composé selon la revendication 1, selon laquelle Ar dans ledit composé est un groupe phényle, m est égal à 0 et R est un groupe halogéno.

7. Utilisation d'un composé selon la revendication 6, selon laquelle R dans ledit composé est un groupe chloro.

50 8. Utilisation d'un composé selon la revendication 1, selon laquelle R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-dans ledit composé représente un groupe 4-chlorophényle, R<sub>1</sub> est un groupe méthyle et R<sub>2</sub> est un groupe éthyle.

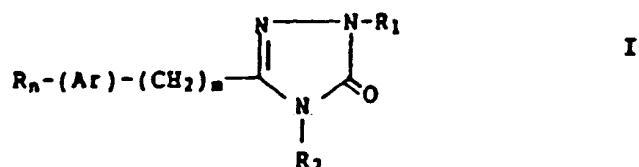
55 9. Utilisation d'un composé selon la revendication 1, selon laquelle R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-dans ledit composé représente un groupe 4-chlorophényle, R<sub>1</sub> est l'hydrogène et R<sub>2</sub> est un groupe éthyle.

10. Utilisation d'un composé selon la revendication 1, selon laquelle  $R_n\text{-(Ar)-(CH}_2)_m$ -dans ledit composé représente un groupe 2-chlorophényle,  $R_1$  est l'hydrogène et  $R_2$  est un groupe méthyle.

11. Un composé de formule

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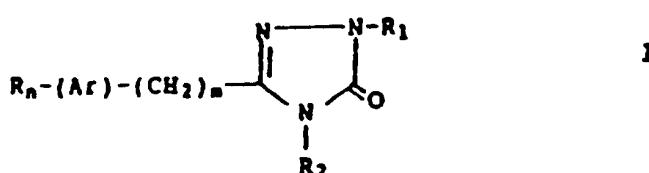
15 dans laquelle

Ar représente un groupe phényle, naphtyle ou une portion hétérocyclique aromatique choisie parmi les suivantes :

20 R<sub>1</sub> est l'hydrogène ou  $C_{1-6}$  alkyle,  
R<sub>2</sub> est  $C_{1-6}$  alkyle,  
R est  $C_{1-6}$  alkyle,  $C_{1-6}$  alcoxy, hydroxy, halogéno ou trifluorométhyle, et  
n est 1 ou 2, ou  
R<sub>n</sub>-(Ar) est méthylénedioxyphényle, et  
25 m est 0, 1 ou 2,  
à la condition que lorsque R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-représente un groupe 4-chlorophényle et R<sub>2</sub> représente un groupe éthyle, R<sub>1</sub> ne peut pas représenter l'hydrogène, et lorsque R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-représente un groupe phényle et R<sub>1</sub> représente un groupe méthyle, R<sub>2</sub> ne peut pas représenter un groupe méthyle ou éthyle, et les sels pharmaceutiquement acceptables des composés dans lesquels Ar est une portion hétérocyclique contenant de l'azote à utiliser comme médicament.

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12. Un composé selon la revendication 11, selon laquelle Ar est un groupe phényle.
13. Un composé selon la revendication 11 ou 12, selon laquelle m est égal à 0.
14. Un composé selon la revendication 11, 12 ou 13, selon laquelle R<sub>2</sub> est un groupe méthyle ou éthyle.
15. Un composé selon la revendication 11, selon laquelle Ar est un groupe phényle, m est égal à 0 et R est un groupe halogéno.
16. Un composé selon la revendication 15, selon laquelle R est un groupe chloro.
17. Un composé selon la revendication 11, selon laquelle R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-représente un groupe 2-chlorophényle, R<sub>1</sub> est l'hydrogène et R<sub>2</sub> est un groupe méthyle.
18. Un composé selon la revendication 11, selon laquelle R<sub>n</sub>-(Ar)-(CH<sub>2</sub>)<sub>m</sub>-représente un groupe 4-chlorophényle, R<sub>1</sub> est un groupe méthyle et R<sub>2</sub> est un groupe éthyle.
19. Un composé de formule I

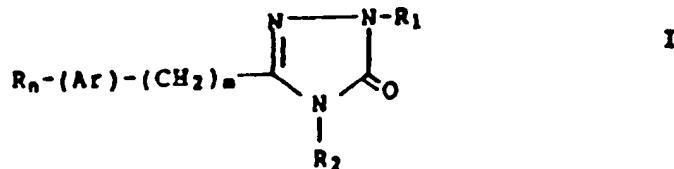
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dans laquelle  $R_n-(Ar)-(CH_2)_m$ -représente un groupe 4-chlorophényle,  $R_1$  est un groupe méthyle et  $R_2$  est un groupe éthyle.

## 20. Un composé de formule I

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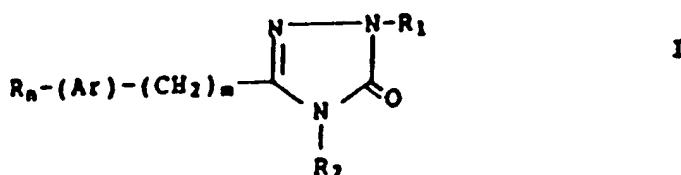


15 dans laquelle  $R_n-(Ar)-(CH_2)_m$ -représente un groupe 2-chlorophényle,  $R_1$  est l'hydrogène et  $R_2$  est un groupe méthyle.

## 21. Une formulation pharmaceutique contenant un composé selon l'une quelconque des revendications 11 à 20 en mélange avec un support pharmaceutique acceptable.

## 22. Un procédé de préparation d'un composé de formule

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dans laquelle  $R_n-(Ar)-(CH_2)_m$ -représente un groupe 4-chlorophényle,  $R_1$  représente un groupe méthyle et  $R_2$  représente un groupe éthyle, qui comprend la réaction d'un semicarbazide de formule IV

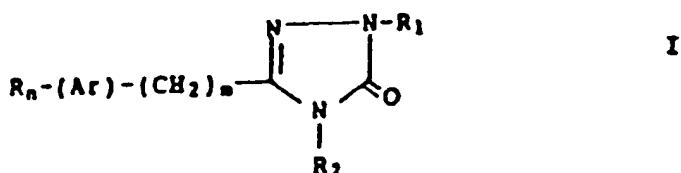
35

$R_n-(Ar)-(CH_2)_mCONHNHCONHR_2$   
dans laquelle  $R_n-(Ar)-(CH_2)_m$ -est comme défini précédemment, avec une base à environ 50 °C-120 °C; et la transformation du produit intermédiaire obtenu dans lequel  $R_1$  représente l'hydrogène en composé de formule I par réaction avec un composé de formule  $R_1X$  dans laquelle X est un bon groupe séparable et  $R_1$  est un groupe méthyle.

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## 23. Un procédé pour la préparation d'un composé de formule

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dans laquelle  $R_n-(Ar)-(CH_2)_m$ -représente un groupe 2-chlorophényle,  $R_1$  représente l'hydrogène et  $R_2$  représente un groupe méthyle qui comprend la réaction d'un semicarbazide de formule IV

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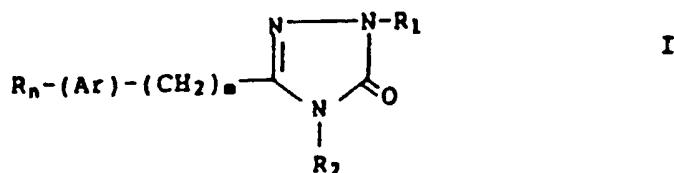
$R_n-(Ar)-(CH_2)_mCONHNHCONHR_2$   
dans laquelle  $R_n-(Ar)-(CH_2)_m$ -est comme défini ci-dessus, avec une base à environ 50 °C-120 °C.

## Revendications pour l'Etat contractant suivant : ES

1. Un procédé de préparation d'un composé de formule

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dans laquelle  $R_n-(Ar)-(CH_2)_m-$  représente un groupe 4-chlorophényle,  $R_1$  représente un groupe méthyle et  $R_2$  représente un groupe éthyle, qui comprend la réaction d'un semicarbazide de formule IV



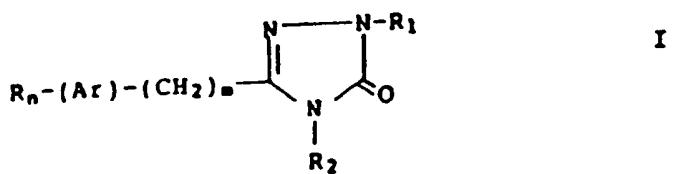
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dans laquelle  $R_n-(Ar)-(CH_2)_m-$  est comme défini précédemment, avec une base à environ 50 °C-120 °C ; et la transformation de l'intermédiaire obtenu dans lequel  $R_1$  représente l'hydrogène en composé de formule I par réaction avec un composé de formule  $R_1X$  dans lequel X est un bon groupe séparable et  $R_1$  est un groupe méthyle.

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2. Un procédé de préparation d'un composé de formule

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dans laquelle  $R_n-(Ar)-(CH_2)_m-$  représente un groupe 2-chlorophényle,  $R_1$  représente l'hydrogène et  $R_2$  représente un groupe méthyle qui comprend la réaction d'un semicarbazide de formule IV



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dans laquelle  $R_n-(Ar)-(CH_2)_m-$  est comme défini précédemment, avec une base à environ 50 °C-120 °C.

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